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(54) Title: BIOLOGICALLY ACTIVE COMPOUNDS

(57) Abstract: Compounds of general formula (I) wherein:  $Z = CR^3R^4$ , where  $R^3$  and  $R^4$  are independently chosen from  $C_{0-7}$ -alkyl  $P_1 = CR^5R^6, P_2 = O, CR^7R^8 \text{ or } NR^9, Y = CR^{10}R^{11} - C(O) \text{ or } CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - S(O) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{16}R^{17} (W)_n = 0, S, CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - SO_2(X)_0 = .CR^{10}R^{11} - C(S) \text{ or } CR^{10}R^{11} - C(S) \text{$  $C(O), S(O) \text{ or } S(O)_2 \text{-or } NR^{18} (V)_m = C(O), C(S), S(O), S(O)_2, S(O)_2NH, OC(O), NHC(O), NHS(O), NHS(O)_2, OC(O)NH, C(O)NH, C(O)$ or CR19R20, C=N-C(O)-OR19 or C=N-C(O)-NHR19, U = a stable. 5- to 7-membered monocyclic or a stable 8- to 11-membered bicyclic ring which is either saturated or unsaturated, and which includes zero to four heteroatoms and their salts, hydrates, solvates, complexes and prodrugs are inhibitors of cathepsin K and other cysteine protease inhibitors and are useful as therapeutic agents, .for example in osteoporosis, Paget's disease gingival diseases such as gingivitis and periodontitis, hypercalaemia of malignancy, metabolic bone disease, diseases involving matrix or cartilage degradation, in particular osteoarthritis and rheumatoid arthritis and neoplastic diseases. The compounds are also useful for validating therapeutic target compounds.





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— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW,

ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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## INTERNATIONAL SEARCH REPORT

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A. CLASSIF IPC 7	CO7D487/04 A61K31/407 A61P19/0	0 A61P35/00						
According to International Patent Classification (IPC) or to both national classification and IPC								
B. FIELDS SEARCHED  Minimum documentation searched (classification system followed by classification symbols)								
IPC 7 C07D								
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched								
Electronic da	tta base consulted during the International search (name of data bas	e and, where practical, search terms used)						
EPO-Internal, WPI Data								
C. DOCUMENTS CONSIDERED TO BE RELEVANT								
Category *	Citation of document, with indication, where appropriate, of the rele	evant passages	Relevant to claim No.					
Р,Х	WO 02 057270 A (INCENTA LTD ;QUIB MARTIN (GB)) 25 July 2002 (2002-0 cited in the application claim 1	1-59						
A	WO 00 69855 A (TAYLOR STEVEN ;MED LTD (GB); QUIBELL MARTIN (GB); PE 23 November 2000 (2000-11-23) the whole document	1–59						
Α	WO 98 50533 A (FENWICK ASHLEY EDW; GRIBBLE ANDREW D (GB); SMITHKLIN P) 12 November 1998 (1998-11-12) the whole document	1–59						
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Further documents are listed in the continuation of box C.  Y  Patent family members are listed in annex.								
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# INTERNATIONAL SEARCH REPORT

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ormation on patent family members

tnb snal Application No PCT/GB 03/02957

Patent document cited in search report		Publication date	•	Patent family member(s)	Publication date
WO 02057270	Α	25-07-2002	WO	02057270 A1	25-07-2002
WO 0069855	Α	23-11-2000	AU	763694 B2	31-07-2003
MO OCCIOCO	••	25 11 2000	ΑÜ	4772200 A	05-12-2000
			BR	0010553 A	02-07-2002
			CA	2374297 A1	23-11-2000
			EP	1178986 A2	13-02-2002
			WO	0069855 A2	23-11-2000
•			JP	2002544274 T	24-12-2002
WO 9850533	Α	12-11-1998	AU	7562598 A	27-11-1998
NO SCOTO			BR	9809306 A	04-07-2000
			CN	1255161 T	31-05-2000
•			EP	1003846 A1	31-05-2000
			HU	0002247 A2	28-05-2001
			JP	2001525804 T	11-12-2001
			NO	995434 A	05-11-1999
			NZ	337889 A	28-09-2001
			PL	336856 A1	17-07-2000
			TR	9902766 T2	21-02-2000
			WO	9850533 A1	12-11-1998
	•		US	2002013360 A1	31-01-2002
			ZA	9803762 A	06-11-1998